HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TENIVAC safely and effectively. See full prescribing information for TENIVAC.

TENIVAC (Tetanus and Diphtheria Toxoids Adsorbed)
Suspension for Intramuscular Injection

Initial US Approval: 2003

---RECENT MAJOR CHANGES---[06/2008]

Indications and Usage (1) • TENIVAC is a vaccine indicated for active immunization for the prevention of tetanus and diphtheria in persons 7 years of age and older.

---DOSE AND ADMINISTRATION---
• Each 0.5 mL dose should be administered intramuscularly. (2.5)
• Primary immunization with TENIVAC consists of 3 doses. The first 2 doses are administered 2 months apart and the third dose is administered 6-8 months after the second dose. (2.1)
• TENIVAC may be used for booster immunization against tetanus and diphtheria. Routine booster immunization against tetanus and diphtheria is recommended at 11-12 years of age and every 10 years thereafter. (2.2)
• For postexposure diphtheria prophylaxis and for management of a tetanus prone wound, a booster dose of TENIVAC may be administered if at least 5 years have elapsed since previous receipt of a diphtheria toxoid and tetanus toxoid containing vaccine. (2.3) (2.4)

---DOSE FORMS AND STRENGTHS---
• Suspension for injection. Each 0.5 mL single dose vial contains tetanus and diphtheria toxoids. (3)

---CONTRAINDICATIONS---
• Severe allergic reaction (e.g., anaphylaxis) to a previous dose of TENIVAC, or any other tetanus or diphtheria toxoid-containing vaccine, or any component of this vaccine. (4.1)

---WARNINGS AND PRECAUTIONS---
• More frequent administration of TENIVAC than described in Dosage and Administration (2.1, 2.2, 2.3, 2.4) may be associated with increased incidence and severity of adverse reactions. (5.2)

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---ADVERSE REACTIONS---
• The most frequent solicited injection site reaction within 0-3 days following TENIVAC was pain, reported in 78.3% of study participants 11-59 years of age and 35.3% of participants ≥60 years of age. (6.1)
• The most frequent solicited systemic reaction within 0-3 days following TENIVAC was headache, reported in 17.9% of participants, overall. (6.1)
• Other common (≥10%) solicited adverse reactions within 0-3 days following TENIVAC were injection site redness, injection site swelling, malaise, muscle weakness and pain in joints. (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact Sanofi Pasteur Inc. at 1-800-822-2463 (1-800-VACCINE) or VAERS at 1-800-822-7967 or http://vaers.hhs.gov

---DRUG INTERACTIONS---
• No safety and immunogenicity data are available on the concomitant administration of TENIVAC with other US licensed vaccines. (7.1)
• If passive protection against tetanus is required, Tetanus Immune Globulin (TIG) (Human) may be administered concomitantly at a separate site with a separate needle and syringe. (7.2)
• Immunosuppressive therapies may reduce the immune response to TENIVAC. (7.3)

---USE IN SPECIFIC POPULATIONS---
Pre- and post-vaccination tetanus and diphtheria seroprotection rates were lower in study participants ≥65 years of age compared to younger participants. In general, rates of solicited adverse reactions were not higher in participants ≥65 years of age compared to younger participants. (8.4)

See 17 for PATIENT COUNSELING INFORMATION
Revised: [June 2008]

*Sections or subsections omitted from the full prescribing information are not listed.
FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TENIVACTM is a vaccine indicated for active immunization for the prevention of tetanus and diphtheria in persons 7 years of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 Primary Immunization

In persons who have not been immunized previously against tetanus and diphtheria, primary immunization with TENIVAC vaccine consists of three 0.5 mL doses. The first 2 doses are administered 2 months apart and the third dose is administered 6-8 months after the second dose.

TENIVAC vaccine may be used to complete the primary immunization series for tetanus and diphtheria, following one or two doses of Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed (whole-cell DTP), Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP), and/or Diphtheria and Tetanus Toxoids Adsorbed (DT). However, the safety and efficacy of TENIVAC vaccine in such regimens have not been evaluated.

2.2 Routine Booster Immunization

TENIVAC vaccine may be used for routine booster immunization against tetanus and diphtheria in persons 7 years of age and older. Routine booster immunization against tetanus and diphtheria is recommended in children 11-12 years of age and every 10 years thereafter. The ACIP (Advisory Committee on Immunization Practices) has specific recommendations on booster immunization against tetanus and diphtheria for adolescents and adults. (1)

2.3 Diphtheria Prophylaxis for Case Contacts

TENIVAC vaccine may be used for post-exposure diphtheria prophylaxis in persons 7 years of age and older who have not completed primary vaccination, whose vaccination status is unknown,
or who have not been vaccinated with diphtheria toxoid within the previous 5 years. Consult
ACIP recommendations for additional interventions for diphtheria prophylaxis in close contacts of
diphtheria patients. (2)

2.4 Tetanus Prophylaxis in Wound Management

For active tetanus immunization in wound management of patients 7 years of age and older, a
preparation containing tetanus and diphtheria toxoids is preferred instead of single-antigen tetanus
toxoid to enhance diphtheria protection. (2) TENIVAC vaccine is approved for wound
management of patients 7 years of age and older.

The need for active immunization with a tetanus toxoid-containing preparation, with or without
passive immunization with Tetanus Immune Globulin (TIG) (Human) depends on both the
condition of the wound and the patient’s vaccination history. (See Table 1.)

When indicated, TIG (Human) should be administered at a separate site, with a separate needle
and syringe, according to the manufacturer’s package insert. If a contraindication to using tetanus
toxoid-containing preparations exists in a person who has not completed a primary immunizing
course of tetanus toxoid and other than a clean, minor wound is sustained, only passive
immunization with TIG (Human) should be given. (2)
Table 1: Summary Guide to Tetanus Prophylaxis in Routine Wound Management for Persons 7 Years of Age and Older (2)

<table>
<thead>
<tr>
<th>History of Adsorbed Tetanus Toxoid (Doses)</th>
<th>Clean, Minor Wounds</th>
<th>All Other Wounds*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown or &lt;three</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>≥Three‡</td>
<td>No§</td>
<td>No**</td>
</tr>
</tbody>
</table>

* Such as, but not limited to, wounds contaminated with dirt, puncture wounds and traumatic wounds.
† Tetanus and Diphtheria Toxoids Adsorbed/Tetanus and Diphtheria Toxoids Adsorbed for Adult Use.
‡ If only three doses of fluid tetanus toxoid have been received, then a fourth dose of toxoid, preferably an adsorbed toxoid should be given.
§ Yes, if >10 years since last dose.
** Yes, if >5 years since last dose. (More frequent boosters are not needed and can accentuate side effects.)

2.5 Administration

Just before use, shake the vial well until a uniform, white, cloudy suspension results. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If these conditions exist, the product should not be administered.

When withdrawing a dose from a rubber-stoppered vial, do not remove either the rubber stopper or the metal seal holding it in place.

Each 0.5 mL dose of TENIVAC vaccine is to be administered intramuscularly. The preferred site is the deltoid muscle. The vaccine should not be injected into the gluteal area or areas where there may be a major nerve trunk.

Do not administer this product intravenously or subcutaneously.

TENIVAC vaccine should not be combined through reconstitution or mixed with any other vaccine.
3 DOSAGE FORMS AND STRENGTHS

TENIVAC vaccine is a suspension for injection of tetanus and diphtheria toxoids in 0.5 mL single-dose vials. [See Description (11).]

4 CONTRAINDICATIONS

4.1 Hypersensitivity

A severe allergic reaction (e.g., anaphylaxis) after a previous dose of TENIVAC vaccine or any other tetanus toxoid or diphtheria toxoid-containing vaccine or any other component of this vaccine is a contraindication to administration of TENIVAC vaccine. [See Description (11).]

Because of uncertainty as to which component of the vaccine may be responsible, none of the components should be administered. Alternatively, such individuals may be referred to an allergist for evaluation if further immunizations are to be considered.

5 WARNINGS AND PRECAUTIONS

5.1 Management of Acute Allergic Reactions

Epinephrine hydrochloride solution (1:1,000) and other appropriate agents and equipment must be available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs.

5.2 Frequency of Administration

More frequent doses of TENIVAC vaccine than described in Section 2, Dosage and Administration, may be associated with increased incidence and severity of adverse reactions. [See Dosage and Administration (2.1, 2.2, 2.3, 2.4).]

5.3 Arthus Reactions

Persons who experienced an Arthus-type hypersensitivity reaction following a prior dose of a
tetanus toxoid-containing vaccine usually have high serum tetanus antitoxin levels and should not receive TENIVAC vaccine more frequently than every 10 years, even for tetanus prophylaxis as part of wound management.

5.4 Guillain-Barré Syndrome and Brachial Neuritis

A review by the Institute of Medicine found evidence for a causal relation between tetanus toxoid and both brachial neuritis and Guillain-Barré syndrome. (3) If Guillain-Barré syndrome occurred within 6 weeks of receipt of prior vaccine containing tetanus toxoid, the decision to give TENIVAC vaccine or any vaccine containing tetanus toxoid should be based on careful consideration of the potential benefits and possible risks. (1)

5.5 Limitations of Vaccine Effectiveness

Vaccination with TENIVAC vaccine may not protect all individuals.

5.6 Altered Immunocompetence

If TENIVAC vaccine is administered to immunocompromised persons, including persons receiving immunosuppressive therapy, the expected immune response may not be obtained. [See Drug Interactions (7.3).]

6 ADVERSE REACTIONS

6.1 Data from Clinical Studies

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to vaccine use and for approximating rates of those events.
In a primary immunization study conducted in Canada, 18 participants, 8 of whom were 6 to 9
years of age and 10 of whom were 17 to 56 years of age, received three doses of a vaccine
formulated the same as TENIVAC vaccine with regard to the tetanus toxoid and diphtheria toxoid
content, but that contained thimerosal and did not contain 2-phenoxyethanol. [See Description
(11).] In four booster immunization studies conducted in either the US or Canada, TENIVAC
vaccine (3,376 participants) or a similar formulation containing thimerosal (347 subjects) was
administered to 3,723 participants overall, ranging in age from 11 to 93 years.

In one of these studies, a US multi-center booster immunization study (TDC01), 2,250
adolescents and adults ages 11-59 years of age received TENIVAC vaccine in an open-label
design and adults 60 years of age and over were randomized to receive either TENIVAC vaccine
(N = 700) or DECAVAC vaccine (US licensed Td manufactured by Sanofi Pasteur Inc.) (N =
701). Vaccine assignment for participants ≥60 years of age was unblinded to pharmacists and
vaccination nurses, but was blinded to other study personnel and participants. Among participants
who received TENIVAC vaccine, overall, 80.4% were Caucasian, 3.3% Black, 5.1% Hispanic,
4.5% Asian and 6.6% other races. Among participants ≥60 years of age, the racial distribution
was similar for the TENIVAC vaccine and DECAVAC vaccine groups. Among participants who
received TENIVAC vaccine, the proportion of participants who were female varied by age group
(44.4% of participants 11-18 years of age, 70.1% of participants 19-59 years of age and 62.4% of
participants ≥60 years of age). Among participants ≥60 years of age who received DECAVAC
vaccine, 57.6% were female. Nearly all (99.8%) enrolled participants and all participants in the
per-protocol immunogenicity population had a reported or documented history of previous
immunization against tetanus and diphtheria and, by report, had not received a vaccine containing
tetanus or diphtheria toxoid within 5 years prior to enrollment.

In the US multi-center booster immunization study, solicited injection site reactions and systemic
adverse events were monitored on diary cards for a subset of participants 11-59 years of age and
for all participants ≥60 years of age. The incidence and severity of solicited injection site
reactions and selected solicited systemic adverse events that occurred within 3 days following
vaccination are shown in Table 2.
Table 2: Frequency and Severity of Selected Solicited Adverse Events Within 0-3 Days Following TENIVAC Vaccine or DECAVAC Vaccine in a US Study

<table>
<thead>
<tr>
<th></th>
<th>TENIVAC Vaccine</th>
<th>DECAVAC Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adolescents 11 to 18 years N = 491-492</td>
<td>Adults 19 to 59 years N = 247</td>
</tr>
<tr>
<td><strong>Injection Site Adverse Reactions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pain</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>80.1</td>
<td>74.9</td>
</tr>
<tr>
<td>Moderate*</td>
<td>15.0</td>
<td>18.2</td>
</tr>
<tr>
<td>Severe†</td>
<td>0.2</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Redness</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>25.6</td>
<td>15.8</td>
</tr>
<tr>
<td>≥35 mm to &lt;50 mm</td>
<td>1.2</td>
<td>2.4</td>
</tr>
<tr>
<td>≥50 mm</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Swelling</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>15.0</td>
<td>17.0</td>
</tr>
<tr>
<td>≥35 mm to &lt;50 mm</td>
<td>1.2</td>
<td>2.8</td>
</tr>
<tr>
<td>≥50 mm</td>
<td>1.8</td>
<td>2.8</td>
</tr>
<tr>
<td><strong>Systemic Adverse Events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fever</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥37.5°C</td>
<td>4.3</td>
<td>5.7</td>
</tr>
<tr>
<td>≥38.0°C to &lt;39°C</td>
<td>0.8</td>
<td>1.6</td>
</tr>
<tr>
<td>≥39°C</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Headache</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>23.0</td>
<td>25.1</td>
</tr>
<tr>
<td>Moderate*</td>
<td>4.3</td>
<td>7.3</td>
</tr>
<tr>
<td>Severe†</td>
<td>0.6</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>Muscle Weakness</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>32.3</td>
<td>17.4</td>
</tr>
<tr>
<td>Moderate*</td>
<td>7.3</td>
<td>3.2</td>
</tr>
<tr>
<td>Severe†</td>
<td>0.6</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>TENIVAC Vaccine</td>
<td>DECAVAC Vaccine</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td></td>
<td>Adolescents 11 to 18 years N = 491-492 %</td>
<td>Adults 19 to 59 years N = 247 %</td>
</tr>
<tr>
<td><strong>Malaise</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>14.5</td>
<td>17.0</td>
</tr>
<tr>
<td>Moderate*</td>
<td>3.5</td>
<td>3.2</td>
</tr>
<tr>
<td>Severe†</td>
<td>0.8</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Pain in Joints</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>15.7</td>
<td>10.9</td>
</tr>
<tr>
<td>Moderate*</td>
<td>2.8</td>
<td>1.6</td>
</tr>
<tr>
<td>Severe†</td>
<td>0.6</td>
<td>0.4</td>
</tr>
</tbody>
</table>

* Moderate: interfered with activities, but did not require medical care or absenteeism.

† Severe: incapacitating, unable to perform usual activities, may have/or required medical care or absenteeism.
In the US booster immunization study, among participants ≥60 years of age, 7 (1.0%) participants in the TENIVAC vaccine group and 10 (1.4%) participants in the DECAVAC vaccine group experienced a serious adverse event within 30 days following vaccination. During this period, 2 (0.3%) participants 19-59 years of age and no participants 11-18 years of age experienced a serious adverse event following TENIVAC vaccine. Serious adverse events within 30 days following TENIVAC vaccine included localized infection, asthma, colonic polyp, cellulitis, angina pectoris, hip and wrist fracture, cholecystitis, chest pain and cerebrovascular accident.

There were five deaths reported during the study. All of the reported deaths were in participants ≥60 years of age and occurred >30 days post-vaccination: three in the TENIVAC vaccine group (cardiopulmonary arrest; myocardial infarction and septic shock; and unknown cause) and two in the DECAVAC vaccine group (myocardial infarction and congestive heart failure; and liver cancer).

In the primary immunization study (N = 18) in which serious adverse events were monitored for 3 days following each vaccination and in three other booster immunization studies in which serious adverse events were monitored for either four days (N = 347) or one month (N = 426) following vaccination, no serious adverse events were reported.

6.2 Data from Post-marketing Experience

The following adverse events have been spontaneously reported during the post-marketing use of TENIVAC vaccine or a similar vaccine manufactured by Sanofi Pasteur Limited with identical antigenic content but that contains thimerosal and does not contain 2-phenoxyethanol. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

The following adverse events were included based on severity, frequency of reporting or the strength of causal association to TENIVAC vaccine:
152 • Blood and lymphatic system disorders
153 Lymphadenopathy
154 • Immune system disorders
155 Allergic reactions (including anaphylactoid reaction, rash, urticaria, pruritus)
156 • Nervous system disorders
157 Paresthesia, dizziness, syncope
158 • Gastrointestinal disorders
159 Vomiting
160 • Musculoskeletal, connective tissue and bone disorders
161 Myalgia, pain in extremities
162 • General disorders and administration site conditions
163 Injection site reactions (including inflammation, mass, edema, induration, warmth, pruritus,
164 cellulitis)
165 Fatigue, edema peripheral

7 DRUG INTERACTIONS

7.1 Concomitant Vaccine Administration

168 No safety and immunogenicity data are available on the concomitant administration of TENIVAC
169 vaccine with other US licensed vaccines.
7.2 Tetanus Immune Globulin (Human)

If passive protection against tetanus is required, TIG (Human) may be administered according to its prescribing information, concomitantly with TENIVAC vaccine at a separate site with a separate needle and syringe. [See Dosage and Administration (2.4).]

7.3 Immunosuppressive Treatments

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs and corticosteroids (used in greater than physiologic doses), may reduce the immune response to TENIVAC vaccine. [See Warnings and Precautions (5.6).]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with TENIVAC vaccine. It is also not known whether TENIVAC vaccine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. TENIVAC vaccine should be given to a pregnant woman only if clearly needed.

Animal fertility studies have not been conducted with TENIVAC vaccine. The effect of TENIVAC vaccine on embryo-fetal and pre-weaning development was evaluated in one developmental toxicity study using pregnant rabbits. Animals were administered TENIVAC vaccine twice prior to gestation, during the period of organogenesis (gestation day 6) and later during pregnancy on gestation day 29, 0.5 mL/rabbit/occasion (a 17-fold increase compared to the human dose of TENIVAC vaccine on a body weight basis), by intramuscular injection. No adverse effects on pregnancy, parturition, lactation, embryo-fetal or pre-weaning development were observed. There were no vaccine related fetal malformations or other evidence of teratogenesis noted in this study.
8.2 Nursing Mothers

It is not known whether TENIVAC vaccine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TENIVAC vaccine is administered to a nursing woman.

8.3 Pediatric Use

TENIVAC vaccine is not approved for use in infants and children younger than 7 years of age. Safety and effectiveness of TENIVAC vaccine in this age group have not been established.

8.4 Geriatric Use

In one clinical study, (TDC01) 449 participants 65 years of age and over, including 192 participants who were 75 years of age and over received a dose of TENIVAC vaccine. A lower proportion of participants 65 years of age and over had a pre-vaccination seroprotective level of antibody to tetanus toxoid and diphtheria toxin compared to adolescents and adults less than 65 years of age. The proportion of participants 65 years of age and over with a seroprotective level of antibody following TENIVAC vaccine was marginally lower for tetanus and lower for diphtheria compared to younger participants. In general, rates of solicited adverse events were not higher in participants 65 years of age and over compared to younger participants. [See Adverse Reactions (6), Clinical Pharmacology (12.1), and Clinical Studies (14.2).]

11 DESCRIPTION

TENIVAC vaccine, Tetanus and Diphtheria Toxoids Adsorbed, is a sterile isotonic suspension of tetanus and diphtheria toxoids adsorbed on aluminum phosphate.
Each 0.5 mL dose of TENIVAC vaccine contains the following active ingredients:

**Tetanus Toxoid**: 5 Lf

**Diphtheria Toxoid**: 2 Lf

Other ingredients per 0.5 mL dose include 1.5 mg of aluminum phosphate (0.33 mg of aluminum) as the adjuvant, ≤0.1 mg of residual formaldehyde and 3.3 mg (0.6 % v/v) of 2-phenoxyethanol (not as a preservative).

*Clostridium tetani* is grown in modified Mueller-Miller casamino acid medium without beef heart infusion. (4) Tetanus toxin is detoxified with formaldehyde and purified by ammonium sulfate fractionation and diafiltration. *Corynebacterium diphtheriae* is grown in modified Mueller’s growth medium. (5) After purification by ammonium sulfate fractionation, diphtheria toxin is detoxified with formaldehyde and diafiltered. Tetanus and diphtheria toxoids are individually adsorbed onto aluminum phosphate.

The adsorbed tetanus and diphtheria toxoids are combined with aluminum phosphate (as adjuvant), 2-phenoxyethanol (not as a preservative), sodium chloride and water for injection.

In the guinea pig potency test, the tetanus toxoid component induces at least 2 neutralizing units/mL of serum and the diphtheria toxoid component induces at least 0.5 neutralizing units/mL of serum.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

**Tetanus**

Tetanus is an acute disease caused by an extremely potent neurotoxin produced by *C tetani*. Protection against disease is due to the development of neutralizing antibodies to tetanus toxin. A serum tetanus antitoxin level of at least 0.01 IU/mL, measured by neutralization assay is considered the minimum protective level. (6) (7) A tetanus antitoxoid level of ≥0.1 IU/mL as
measured by the ELISA used in some clinical studies of TENIVAC vaccine is considered protective.

Diphtheria

Diphtheria is an acute toxin-mediated disease caused by toxigenic strains of *C. diphtheriae*. Protection against disease is due to the development of neutralizing antibodies to diphtheria toxin. A serum diphtheria antitoxin level of 0.01 IU/mL is the lowest level giving some degree of protection. Antitoxin levels of at least 0.1 IU/mL are generally regarded as protective. (6) A level of at least 1.0 IU/mL has been associated with long-term protection. (8)

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

TENIVAC vaccine has not been evaluated for carcinogenic or mutagenic potential or impairment of fertility.

14 CLINICAL STUDIES

14.1 Primary Immunization

A three-dose primary immunization series with a vaccine containing the same tetanus toxoid and diphtheria toxoid as in TENIVAC vaccine but that contained thimerosal and not 2-phenoxyethanol, was evaluated in 17 participants ages 6 to 56 years in a study conducted in Canada. [See Adverse Reactions (6.1).] The first two doses were administered two months apart, followed by a third dose six to eight months after the second dose. Serum tetanus antitoxin levels were measured by an *in vivo* neutralizing assay and serum diphtheria antitoxin levels were measured by an *in vitro* neutralizing assay. [See Clinical Pharmacology (12.1).] All 17 participants had serum tetanus and diphtheria antitoxin levels pre-vaccination and 7 days post-vaccination <0.01 IU/mL, consistent with no previous immunization. Four weeks following the second dose, all 17 participants had a serum tetanus antitoxin level >0.1 IU/mL and a serum diphtheria antitoxin level ≥0.01 IU/mL. Four weeks following the third dose, all 17 participants had a serum diphtheria antitoxin level >0.1 IU/mL.
14.2 Booster Immunization

In the US multicenter booster immunization study (TDC01) [see Adverse Reactions (6.1)], the immune response to a dose of TENIVAC vaccine was evaluated in an open-label manner in a subset of participants 11 to 59 years of age, and in comparison to DECAVAC vaccine in participants ≥60 years of age who were randomized to receive a dose of either TENIVAC vaccine or DECAVAC vaccine. Tetanus immune responses, measured by ELISA [see Clinical Pharmacology (12.1)] are presented in Table 3. Diphtheria immune responses, measured by a microneutralization assay [see Clinical Pharmacology (12.1)], are presented in Table 4.

Among adults 65 years of age and over who received TENIVAC vaccine (N = 419), 94.5% (95% confidence interval 91.9, 96.5) had a post-vaccination tetanus antitoxoid level ≥0.1 IU/mL and 61.1% (95% confidence interval 56.2, 65.8) had a post-vaccination diphtheria antitoxoid level ≥0.1 IU/mL.
Table 3: Tetanus Antitoxoid Levels and Booster Response Rates Following a Dose of TENIVAC Vaccine, by Age Group, and for Adults ≥60 Years of Age, Compared to DECAVAC Vaccine, per Protocol Immunogenicity Population

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Age Group</th>
<th>Timing</th>
<th>Percent of Participants With Specified Level of Tetanus Antitoxoid and Booster Response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥0.1 IU/mL % (95% CI)</td>
</tr>
<tr>
<td>TENIVAC vaccine</td>
<td>Adolescents Pre-11 to 18 years (N = 470)</td>
<td>Pre-</td>
<td>97.9 (96.1, 99.0)</td>
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<tr>
<td></td>
<td></td>
<td>Post-</td>
<td>100.0 (99.2, 100)</td>
</tr>
<tr>
<td></td>
<td>Adults Pre-19 to 59 years (N = 237)</td>
<td></td>
<td>97.5 (94.6, 99.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-</td>
<td>100.0 (98.5, 100)</td>
</tr>
<tr>
<td></td>
<td>Adults Pre-≥60 years (N = 661)</td>
<td></td>
<td>76.2 (72.8, 79.4)</td>
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<tr>
<td></td>
<td></td>
<td>Post-</td>
<td>96.1† (94.3, 97.4)</td>
</tr>
<tr>
<td>DECAVAC vaccine</td>
<td>Adults Pre-≥60 years (N = 658)</td>
<td></td>
<td>75.2 (71.7, 78.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-</td>
<td>97.3 (95.7, 98.4)</td>
</tr>
</tbody>
</table>

* Booster response: If pre-vaccination level ≤0.10 IU/mL, 4-fold increase and post-vaccination level ≥0.10 IU/mL. If pre-vaccination level >0.10 IU/mL and ≤2.7 IU/mL, 4-fold increase. If pre-vaccination level >2.7 IU/mL, 2-fold increase.

† TENIVAC vaccine non-inferior to DECAVAC vaccine [upper limit of 95% CI for difference (DECAVAC vaccine minus TENIVAC vaccine) <5%].

‡ Non-inferiority criteria not prospectively specified for this endpoint.

§ TENIVAC vaccine non-inferior to DECAVAC vaccine [upper limit of 95% CI for difference (DECAVAC vaccine minus TENIVAC vaccine) <10%].

Pre- indicates pre-vaccination bleed.
Post- indicates 26-42 days post-vaccination bleed.
## Table 4: Diphtheria Antitoxin Levels and Booster Response Rates Following a Dose of TENIVAC Vaccine, by Age Group, and for Adults ≥60 Years of Age, Compared to DECAVAC Vaccine, per Protocol Immunogenicity Population

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Age Group</th>
<th>Timing</th>
<th>Percent of Participants With Specified Level of Diphtheria Antitoxin and Booster Response</th>
<th>Booster Response* % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥0.01 IU/mL % (95% CI)</td>
<td>≥0.1 IU/mL % (95% CI)</td>
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<td></td>
<td></td>
<td>≥1.0 IU/mL % (95% CI)</td>
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<tr>
<td>TENIVAC vaccine</td>
<td>Adolescents 11 to 18 years (N = 470)</td>
<td>Pre-</td>
<td>99.1 (97.8, 99.8)</td>
<td>78.7 (74.7, 82.3)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>18.5 (15.1, 22.3)</td>
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<td></td>
<td></td>
<td>100.0 (99.2, 100)</td>
<td>99.8 (98.8, 100)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>98.9 (97.5, 99.7)</td>
</tr>
<tr>
<td></td>
<td>Adults 19 to 59 years (N = 237)</td>
<td>Pre-</td>
<td>96.6 (93.5, 98.5)</td>
<td>73.0 (66.9, 78.5)</td>
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<td></td>
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<td></td>
<td></td>
<td>18.6 (13.8, 24.1)</td>
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<td></td>
<td>99.2 (97.0, 99.9)</td>
<td>97.5 (94.6, 99.1)</td>
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<td></td>
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<td></td>
<td></td>
<td>91.1 (86.8, 94.4)</td>
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<td></td>
<td>Adults ≥60 years (N = 661)</td>
<td>Pre-</td>
<td>61.9 (58.1, 65.6)</td>
<td>29.0 (25.6, 32.7)</td>
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<td>8.5 (6.5, 10.9)</td>
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<td></td>
<td>88.0† (85.3, 90.4)</td>
<td>71.1‡ (67.5, 74.5)</td>
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<td></td>
<td></td>
<td>47.5† (43.6, 51.4)</td>
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<tr>
<td>DECAVAC vaccine</td>
<td>Adults ≥60 years (N = 658)</td>
<td>Pre-</td>
<td>61.7 (57.9, 65.4)</td>
<td>32.2 (28.7, 35.9)</td>
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<td>10.5 (8.3, 13.1)</td>
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<td>87.4 (84.6, 89.8)</td>
<td>70.7 (67.0, 74.1)</td>
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<td>45.7 (41.9, 49.6)</td>
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</table>

* Booster response: If pre-vaccination level ≤0.10 IU/mL, 4-fold increase and post-vaccination level ≥0.10 IU/mL. If pre-vaccination level >0.10 IU/mL and ≤2.56 IU/mL, 4-fold increase. If pre-vaccination level >2.56 IU/mL, 2-fold increase.

† Non-inferiority criteria not prospectively specified for this endpoint.

‡ TENIVAC vaccine non-inferior to DECAVAC vaccine [upper limit of 95% CI for difference (DECAVAC vaccine minus TENIVAC vaccine) <10%].

Pre- indicates pre-vaccination bleed.
Post- indicates 26-42 days post-vaccination bleed.
REFERENCES


6 FDA. Department of Health and Human Services (DHHS). Biological products; bacterial vaccines and toxoids; implementation of efficacy review; proposed rule. Fed Reg 1985;50(240):51002-117.


HOW SUPPLIED/STORAGE AND HANDLING
302 Vial, 1 dose (10 per package) - NDC No. 49281-210-11

303 The vial stopper does not contain latex.

304 TENIVAC vaccine should be stored at 2° to 8°C (35° to 46°F). DO NOT FREEZE. Product which has been exposed to freezing should not be used. Do not use after expiration date shown on the label.

17 PATIENT COUNSELING INFORMATION

308 Before administration of TENIVAC vaccine health-care providers should inform the patient, parent or guardian of the benefits and risks of the vaccine and the importance of completing the primary immunization series or receiving recommended booster doses, as appropriate, unless a contraindication to further immunization exists.

312 The health-care provider should inform the patient, parent or guardian about the potential for adverse reactions that have been temporally associated with TENIVAC vaccine or other vaccines containing similar components. The health-care provider should provide the Vaccine Information Statements (VISs) which are required by the National Childhood Vaccine Injury Act of 1986 to be given with each immunization. Patients, parents, or guardians should be instructed to report adverse reactions to their health-care provider.

318 Printed in Canada

319 Product information as of June 2008.

320 Manufactured by:

321 Sanofi Pasteur Limited

322 Toronto Ontario Canada
Distributed by:

Sanofi Pasteur Inc.

Swiftwater PA 18370 USA

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